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Poster

ARRY-162, A Potent and Selective MEK 1 / 2 Inhibitor, Shows Enhanced Efficacy in Combination with Other Targeted Kinase Inhibitors and with Chemotherapy

Array BioPharma

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Corresponding author: Array BioPharma, array.bio@cureus.com

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Abstract

MAPK kinase pathway-activation is implicated in uncontrolled cell proliferation and tumor growth in numerous tumor types. Targeting MEK may inhibit cancer cell signaling mediated by a wide variety of signals, making MEK an attractive target for the treatment of cancer. Recent data suggest that some cancers are resistant/refractory to MEK inhibitors due to activation of alternate pathways. Optimal efficacy may require inhibition of additional pathways. We report activity of the MEK inhibitor ARRY-162, in combination with inhibitors of mTOR and the ErbB receptor family as well as standard-of-care chemotherapeutics, in various tumor xenograft models.ARRY-162 is a novel, potent and selective allosteric MEK inhibitor that has entered clinical development for the treatment of cancer. In vivo, ARRY-162 is efficacious in numerous tumor xenograftmodels that harbor BRAF or KRAS mutations. ARRY-162 activity, alone and in combination with, an mTOR inhibitor (ARR-mTOR-1) was evaluated in A549 (KRAS mutant) and in NCI-H460 (KRAS mutant and constitutively active PI3K) models. In A549, both ARRY-162 and ARR-mTOR-1, as single agents, produced significant tumor growth inhibition (TGI; 71 and 82%, respectively). Enhanced inhibition (89% TGI) and regressions were seen when these agents were given in combination. In NCI-H460, ARRY-162 alone was inactive while ARR-mTOR-1 showed moderate activity (64 %TGI). Combination of these treatments enhanced TGI and produced significant tumor growth delay confirming recent reports that mTor pathway activation confers resistance to MEK inhibitors. The LoVo CRC model (KRAS mutant and pEGFR overexpression) has demonstrated resistance to EGFR-targeted therapies (i.e., cetuximab). In LoVo xenografts, ARRY-162 produced modest TGI (50%) as did ARRY-543, a pan-ErbB KI (57% TGI), with no tumor regressions in either single agent group. Combination treatment produced 83% TGI with 3 partial responses (>50% tumor regression). Thus, combining ARRY-162 with agents that inhibit signaling through the ErbB pathway produced additive efficacy and significant regressions. Lastly, the activity of ARRY-162 in combination with gemcitabine or paclitaxel was determined. ARRY-162 alone produced 40 and 79% TGI while gemcitabine or paclitaxel alone achieved 16% and 43%

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TGI in MiaPaCa or COLO 205 xenografts, respectively. When dosed as combinations in either model, TGI was enhanced and regressions were achieved. Thus, ARRY-162 has demonstrated significant single agent activity as well as promising additivity with anti-cancer agents. The added activity in these wide-ranging models with many different chemotherapeutics suggests a large versatility may be expected when this drug is used in combination in the clinic.

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